Attorney's Docket No. 007157/239838 (5543-17) PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	Stein *et al.*	Confirmation No.:	5877
Appl. No.:	09/973,375	Group Art Unit:	1617
Filed:	10/9/01	Examiner:	S. Jiang
For:	METHODS FOR THE TREATMENT OF A TRAUMATIC CENTRAL NERVOUS SYSTEM INJURY		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RULE 37 C.F.R. § 1.132 DECLARATION
of
Dr. David W. Wright

Sir:

I, Dr. David W. Wright, M.D., do hereby declare and say as follows:

1. I am skilled in the art of the field of the invention. I have an M.D. degree from the University of Alabama School of Medicine. I have a Bachelor of Science degree in Biology from Samford University. I have post-doctoral training in Emergency Medicine from the University of Cincinnati. Since 1997, I have been engaged in the study of neuroinjury, and particularly the study of nuerosteroids and traumatic brain injury. I am a past Howard Huges Fellow and have been employed by the Department of Emergency Medicine at Emory University since 1997. Presently, I am the Assistant Director of Emergency Medicine Center (EMRC) and the Director of the Emory Brain Injury Research Group.

2. I have read and understood the Office Actions in the above case dated July 1, 2003, April 14, 2003, November 20, 2002, and April 23, 2002. I have also read and understood references cited and discussed in this case, including Gee *et al.* (RE 35,517), Roof *et al.* (1994) *Experimental Neurology 129*:64-69; Roof *et al.* (1992) *Restorative Neurology and Neuroscience 4*:425-427; Roof *et al.* (1997) *Molecular and Chemical Neuropathology 31*:1-11; and, U.S. Patent No. 5,068,226.

3. The July 1, 2003 Office Action, along with the preceding actions, contain inaccurate conclusions regarding the teachings of the references referred to above. Below is a summary of the teachings provided in each of the references.

a. Gee *et al.* performs *in vitro* binding studies and demonstrates that certain progesterone metabolites, including allopregnanolone, interact with the GABA/GBR complex at sites that are distinct from the site of interaction of barbiturates and other characterized modulators of GABA/GBR activity. See, Table 2 and Figures 1-3. Gee *et al.* also perform *in vivo* studies in which mice were administered a progesterone metabolite and 10 minutes later TBPS was injected into the mouse, resulting in TBPS-induced convulsions. The time to onset of myoclonus (presence of forelimb clonic activity) was assayed (see, column 15 and 16). Figure 4 demonstrates that certain progesterone metabolites, including allopregnanolone, significantly delayed the onset of myoclonus. As stated in column 15 lines 34-40, "the rank order potency and efficacy of these steroids *in vivo* were well correlated with the values determined *in vitro*".

b. The teachings of Roof *et al.* (1994) begin with the presumptions from previous studies that concluded progesterone reduces cerebral edema after traumatic brain injury in rats. Roof *et al.* (1994) teach that progesterone treated animals perform better on a behavioral task that measures spatial navigation ability (Morris water maze) and have less neuronal degeneration in the medial dorsal thalamic nucleus at 21 days post injury than untreated animals after contusion injury to the bilateral medial frontal cortex. The study summarizes that progesterone improves behavioral outcome (on at least one task) and prevents neuronal cell loss. The authors hypothesize that the improvement in neurological function may be due to progesterone's effect on decreasing brain edema after traumatic brain injury. Other possible mechanisms are mentioned, but not proven in this manuscript. There is no mention of the exact mechanism of action or of GABA receptor activation. There is no reference to progesterone metabolites.

c. Roof *et al.* (1992) teach that progesterone treatment (4mg/kg) decreases cerebral edema when administered after a traumatic brain injury. The mechanism of action is not identified. Roof *et al.* postulate that interaction with the Na-K+ ATPase pump may be one mechanism for inhibiting the post TBI edema. They do not mention GABA receptors or progesterone metabolites.

d. Roof *et al.* (1997) teach that progesterone decreases 8-isoPGF2 levels in rat brains after injury and suggests that one mechanism of action may be through antioxidant properties. Roof *et al.* deduce that antioxidant properties would protect the blood brain barrier and hence decrease cerebral edema. Roof *et al.* expound on other possible mechanisms for progesterone's neuroprotective properties, including GABA and glutamate receptor potentiation, radical savaging, and membrane stabilization (page 7, paragraphs 2 and 30), but does not prove these mechanisms of action nor do they even suggest that they are fact.

4. I disagree with many of the scientific conclusions appearing in the Office Action mailed July 1, 2003. Each of the disputed scientific conclusions is addressed individually below.

a. The July 1, 2003 Office Action asserts "Gee et al. also discloses that the beneficial effects of progesterone is related to the conversion of progesterone to the active metabolites and derivatives including allopregnanolone since the metabolites and derivatives possess higher potency and efficacy than progesterone". (Office Action, page 5, paragraph 2, lines 9-11.)

I disagree with this conclusion. Gee *et al.* teach that both progesterone and many of its metabolites bind with high affinity to a unique GABA/GBR complex and that these metabolites delay onset of myoclonus following TBPS induced seizures in mice. There is no data demonstrating that progesterone and allopregnanolone are effective at treating other disease states, such as traumatic brain injury, and certainly no teaching that *all* of progesterone's beneficial effects are related to progesterone's conversion into its various metabolites.

b. Page 4 of the July 1, 2003 Office Action states that Roof *et al.* (1997) teaches "progesterone's neuroprotective effects are through its interaction with GABA" (emphasis in original).

I disagree with this conclusion. We know now that GABA is unlikely to be the sole mechanism by which progesterone provides neuroprotection. While, Roof *et al.* (1997) teach that progesterone decreases 8-isoPGF2 levels in rat brains after injury and suggests that one mechanism of action may be through antioxidant properties, Roof *et al.* expound on other possible mechanisms for progesterone's neuroprotective properties, including GABA and

glutamate receptor potentiation, radical savaging, and membrane stabilization (page 7, paragraphs 2 and 30). Thus, while Roof *et al.* hypothesize that GABA may be one mechanism of action for the neuroprotective effect of progesterone, Roof *et al.* does not assert that it is the only mechanism of action nor does Roof *et al.* prove that this is even a real mechanism of action. This fact is even acknowledged on page 7, lines 21-23 of Roof *et al.* (1997) that states, "We are activity investigating, *but have not yet determined*, the specific mechanism for progesterone's antioxidant effect (emphasis added). Accordingly, contrary to the conclusion in the Office Action, Roof *et al.* (1997) fails to demonstrate the actual mechanism of action by which progesterone is mediating its neuroprotective effect.

c. The July 1, 2003 Office Action asserts that Roof *et al.* teach progesterone and its metabolites, such as allopregnanolone, are known to share the same mechanism of action on their neuroprotective effects (Office Action, page 5, paragraph 2, lines 11-14).

As outlined above in section 4b, the work of Roof *et al.* (1997) never teaches the mechanisms of action by which progesterone is mediating its neuroprotective effects. Therefore, it is impossible to conclude that Roof *et al.* (1997) teaches that progesterone and its metabolites are know to share the same mechanism of action for their neuroprotective properties.

Moreover, it is presumptuous to assume that both allopregnanolone and progesterone have the same mechanisms of action for their neuroprotective effects. Allopregnanolone and progesterone are distinct chemical compounds that may have unique properties and mechanisms of action. Assuming that compounds with similar precursors or structure have identical mechanism of action is flawed and incompatible with known scientific data. Further investigation into the exact mechanisms of action of allopregnanolone and progesterone is required before this conclusion can be rendered.

Four lines of evidence are provided below that demonstrate equating the mechanism of action of progesterone and allopregnanolone is inappropriate.

i) It was presumed that medroxyprogesterone (a synthetic progestin) had identical effects as progesterone, however, it is now becoming clear that medroxyprogesterone behaves very differently than natural progesterone and the presumption that they were the same has potentially lead to erroneous results in clinical trials. See, for example, Nilsen *et al.* (2003) *Endocrionlogy* 143:205-212, provided herewith in Appendix A.

ii) A stable analog of progesterone (i.e., which does not metabolize to allopregnanolone), promegestone, indicates that it is as protective as progesterone (Pham *et al.* (2003) 21st Annul National Neurotrauma Society Symposium Abstract P133). This indicates that progesterone and allopregnanolone participate in a separate pathways that mediate neuroprotection. Pham *et al.* is provided in Appendix B.

iii) Ghoumri *et al.* (2003) *J. Neurochem 86*:848-59 demonstrated that progesterone, promegestone, and allopregnanolone all promote remyelination. However, bicurium treatment blocks the effects of allopregnanolone but not progesterone or promegestone, demonstrating different mechanisms of action. Ghoumri *et al.* is provided in Appendix C.

iv) Allopregnanolone does not appear to bind to the putative progesterone membrane receptor or to the sigma receptor (Krebs *et al.* (2000) *Proc. Natl. Acad. Sci. USA 97*:12816-21 and Monnet *et al.* (1995) *Proc. Natl. Acad. Sci U.S.A. 92*:3774-8). In addition, allopregnanolone still mediates its effects in the absence of the classical steroid receptor in knockout mice (Fry *et al.* (1999) *Brain Res 815*:259-69). Thus the effects of allopregnanolone would not be determined to act via the same mechanism Krebs *et al.*, Monnet *et al.* and Fry *et al.* are provided in Appendices D, E, and F, respectively.

Each of the examples presented above in sections 4c i)-iv) show that allopregnanolone is a unique compound and has different mechanisms of action from its parent compound, progesterone. Therefore, contrary to the conclusions appearing in the Office Action, one of skill would not conclude that progesterone and its metabolites, such as allopregnanolone, are known to share the same mechanism of action.

d. The July 1, 2003 Office Action states that Roof *et al.* (1997) teach "progesterone and its metabolites such as allopregnanolone are known to share the same mechanism of action on their neuroprotective effects through their interaction with GABA" (Office Action, page 5, paragraph 2, lines 11-14).

This statement is scientifically inaccurate. As outlined above, Roof *et al.* (1997) does not render this conclusion. Roof *et al.* (1997) teach that progesterone decreases 8-isoPGF2 levels in rat brains after injury and suggests that one mechanism of action may be through its antioxidant properties. As discussed above, Roof *et al.* expound on other possible mechanisms for progesterone's neuroprotective properties, including GABA and glutamate receptor

potentiation, radical savaging, and membrane stabilization (page 7, paragraphs 2 and 30), Roof *et al.* does not prove that these are the actual mechanisms of action nor do they even suggest that they are fact. The only mention of progesterone metabolites by Roof *et al.* (1997) is restating known evidence that progesterone and some of its metabolites are known to bind to and potentiate activity at the GABAa Receptor. Therefore, Roof *et al.* neither teaches nor asserts that progesterone or its metabolites are working solely through the GABA receptor to promote recovery from brain injury. Roof *et al.* also does not specifically mention allopregnanolone and therefore does not teach anything specific to this compound and does not assert that the mechanism of action of progesterone's metabolites are identical. Accordingly, the conclusions in the Office Action are incorrect.

e. The July 1, 2003 Office Action asserts that one of ordinary skill in the art would conclude that allopregnanolone has "the same therapeutic usefulness as progesterone in the CNS" (page 6, lines 2-3, emphasis in original).

This is also an inaccurate scientific conclusion. As discussed in detail above in sections 4a, 4b, 4c, and 4d, none of the references cited by the Examiner render this conclusion.

It is further noted that no art to date has demonstrated that progesterone and allopregnanolone have identical mechanisms of action for the treatment of traumatic brain injury. It has been shown that progesterone and allopregnanolone share an affinity for the GABA receptor. However, since the mechanism for progesterone's neuroprotection is unlikely to be solely though the GABA receptor, it is not reasonable to assign identical mechanisms of action for both compounds nor assume that they share exact phenotypic properties. Accordingly, contrary to the assertion in the Office Action, one of skill, in view of the present understanding of the functional differences between progesterone allopregnanolone, would not conclude that progesterone and allopregnanolone have the same therapeutic usefulness.

f. The Examiner continues to imply that the modulation of GABA receptors is equivalent to the treatment of a traumatic brain injury.

This is an inaccurate scientific conclusion. Modulation of the GABA receptor is likely to play only a very small role in the treatment of traumatic brain injury . Those familiar with traumatic brain injury research know that treatment with selective GABA agonist (i.e.

valium, ativan, etc.) do not infer neuroprotection alone. Recent research has clearly demonstrated a complex cascade of events leading to progression of neuronal death and extension of injury after a traumatic brain injury. No selective GABA agonist has proven to significantly alter this course. Accordingly, one of skill would not conclude modulating GABA receptor and treatment of a traumatic brain injury to be equivalent biological processes.

5. For the above reasons, based on my education and scientific experience, I believe that the claimed invention is new and not obvious in view of the prior art cited.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 12/10/03 By: _____

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